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UTILITY PATENT APPLICATION TRANSMITTAL <small>See MPEP chapter 600 concerning utility patent application contents</small>		Attorney Docket No. 36780028US04	
		First Named Inventor or Application Identifier William Pendergast	
		Title Method of Promoting Cervical and Vaginal Secretions	
		Express Mail Label No. EL514780509US	
APPLICATION ELEMENTS		Assistant Commissioner for Patents ADDRESS TO: Box Patent Application Washington, DC 20231	
1. <input checked="" type="checkbox"/> *Fee Transmittal Form (Form PTO-1082) (Submit an original and a duplicate for fee processing)		6. <input type="checkbox"/> Microfiche Computer Program (Appendix)	
2. <input checked="" type="checkbox"/> Specification [Total Pages 32] (preferred arrangement set forth below) <ul style="list-style-type: none">- Descriptive title of the Invention- Cross References to Related Applications- Statement Regarding Fed sponsored R&D- Reference to Microfiche Appendix- Background of the Invention- Brief Summary of the Invention- Brief Description of the Drawings (if filed)- Detailed Description- Claims- Abstract of the Disclosure <input type="checkbox"/> Drawing(s) (35 USC 113) [Total Sheets] Oath or Declaration [Total Pages 2] <ul style="list-style-type: none">a. <input type="checkbox"/> Newly executed (original or copy)b. <input checked="" type="checkbox"/> Copy from a prior application (37 CFR 1.63(d)) (for continuation/divisional with Box 17 completed) [Note Box 5 below]i. <input type="checkbox"/> DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).		7. Nucleotide and/or Amino Acid Sequence Submission (if applicable, all necessary) <ul style="list-style-type: none">a. <input type="checkbox"/> Computer Readable Copyb. <input type="checkbox"/> Paper Copy (identical to computer copy)c. <input type="checkbox"/> Statement verifying identity of above copies	
		ACCOMPANYING APPLICATION PARTS	
		8. <input type="checkbox"/> Assignment Papers (cover sheet & document(s))	
		9. <input type="checkbox"/> 37 CFR 3.73(b) Statement <input type="checkbox"/> Power of Attorney (when there is an assignee)	
		10. <input type="checkbox"/> English Translation Document (if applicable)	
		11. <input type="checkbox"/> Information Disclosure Statement (IDS)/PTO-1449 <input type="checkbox"/> Copies of IDS Citations	
		12. <input type="checkbox"/> Preliminary Amendment	
		13. <input checked="" type="checkbox"/> Return Receipt Postcard (MPEP 503) (Two) (should be specifically itemized)	
		14. <input type="checkbox"/> *Small Entity Statement(s) <input type="checkbox"/> Statement filed in prior application, Status still proper and desired	
		15. <input type="checkbox"/> Certified Copy of Priority Document(s) (if foreign priority is claimed)	
		16. <input type="checkbox"/> Other:	
5. <input checked="" type="checkbox"/> Incorporation By Reference (useable if Box 4b is checked) The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.		*NOTE FOR ITEMS 1 & 14 IN ORDER TO BE ENTITLED TO PAY SMALL ENTITY FEES, A SMALL ENTITY STATEMENT IS REQUIRED (37 C.F.R. § 1.27), EXCEPT IF ONE FILED IN A PRIOR APPLICATION IS RELIED UPON (37 C.F.R. § 1.28)	
17. If a CONTINUING APPLICATION , check appropriate box and supply the requisite information: <input checked="" type="checkbox"/> Continuation <input type="checkbox"/> Divisional <input type="checkbox"/> Continuation-in-part (CIP) of prior application No: 09/199,912 Prior Application Information: Examiner: Kunz, G. Group/Art Unit: 1623			
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FORM PTO-1082

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Attorney Docket No. 36780028US04

Box Patent Application

ASSISTANT COMMISSIONER FOR PATENTS
Washington, D.C. 20231

Sir:

Transmitted herewith for filing is the patent application of William PENDERGAST, Sammy R. SHAVER, David J. DRUTZ, and Janet L. RIDEOUT for **METHOD OF PROMOTING CERVICAL AND VAGINAL SECRECTIONS**.

Also, enclosed are:

1. Copy of Combined Declaration and Power of Attorney for Patent Application (2 pages);
2. Two (2) return postcards.

The filing fee has been calculated as shown below:

	(Col. 1)	(Col. 2)
FOR	NO. FILED	NO. EXTRA
BASIC FEE		
TOTAL CLAIMS	22 - 20 =	* 2
INDEP. CLAIMS	1 - 3 =	* 0
<input checked="" type="checkbox"/> MULTIPLE DEPENDENT CLAIM PRESENTED		

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SMALL ENTITY	
RATE	FEE
x 9 =	
x 39 =	
+ 130 =	
TOTAL	

OTHER THAN A SMALL ENTITY	
RATE	FEE
	\$ 690.00
2 X 18 =	36.00
X 78 =	0.00
+ 260 =	\$ 260.00
TOTAL	\$ 986.00

This application is being filed under 37 C.F.R. §1.53(b)(1) without filing fee. This application is a continuation of U.S. Application Serial No. 09/199,912 filed November 25, 1998, which is a continuation-in-part of U.S. Application Serial No. 09/122,516, filed July 24, 1998, which claims priority to U.S. Provisional Application Serial No. 60/054,147, filed July 25, 1997.

Date: March 20, 2000


ALBERT P. HALLUIN (Reg. No. 25,227)

COPY

PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

METHOD OF PROMOTING CERVICAL AND VAGINAL SECRETIONS

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Attorney's Docket No. 36780028 US2

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METHOD OF PROMOTING CERVICAL AND VAGINAL SECRETIONS

This application is a continuation-in-part of U.S. Application Serial No. 09/122,516 filed July 24, 1998, which claims priority to U.S. Provisional Application
5 Serial No. 60/054,147, filed July 25, 1997. Both applications are incorporated herein by reference.

TECHNICAL FIELD

This invention relates to a method of regulating secretions in and around
10 the cervix and vagina of a patient by administering purinergic receptor agonists such as certain uridine, adenine, or cytidine triphosphates as well as other nucleoside phosphate containing compounds.

BACKGROUND OF THE INVENTION

15 Vaginal dryness is a very common problem which brings physical and emotional distress to many women (Key, E., *Nurs. Stand.* 5:24-27 (1991)). It most commonly manifests itself during sexual intercourse, which causes dyspareunia and can eventually lead to apareunia. Although it is traditionally considered to be a condition which affects postmenopausal women, it can occur during the
20 premenopausal and perimenopausal years. The use of oral contraceptives may also cause a reduction in vaginal moisture in some women (Reginald, W., *et al.*, *Br. J. Obstet. Gynaecol.* 96:1148-1152 (1989)). Postpartum vaginal dryness, independent of or as a result of lactation, can be a significant complaint (Wisniewski, P., *et al.*, *Am. J. Obstet. Gynecol.* 165:1249-1254 (1991)). Women undergoing chemotherapy or
25 radiotherapy for malignant diseases such as leukemia often experience vaginal dryness as a result of treatment (Cust, M., *et al.*, *Br. Med. J.* 299:1494-1497 (1989)). Many disease states, such as systemic sclerosis and other systemic autoimmune disorders (Bhadauria, S., *et al.*, *Am. J. Obstet. Gynecol.* 172:580-587 (1995)), Ehlers-Danlos syndrome (Sorokin, Y., *et al.*, *J. Reprod. Med.* 39:281-284 (1994)), diabetes

mellitus (Sreebny, L., *et al.*, *Diabetes Care* 15:900-904 (1992)), and Sjögren's syndrome (Marchesoni, D., *et al.*, *Eur. J. Obstet. Gynecol. Reprod. Biol.* 63:49-53 (1995)) have decreased vaginal hydration and lubrication problems as significant disease-associated symptoms.

5 Vulvar pain is defined as the excessive sensitivity of the nerves supplying the mucus membrane of the vulva. This persistent burning and sensitivity in vulvar skin is not caused by identifiable infection. It cannot be cured by surgery. The diseases covered under "vulvar pain" are also referred to as vulvodynia/vulvar vestibulitis, vulvitis, burning vulvar syndrome and is often associated with

10 fibromyalgia, irritable bowel syndrome, Sjögren's syndrome, chronic inflammation, and Paget's disease as well as in the absence of any identifiable disease or infection. R. Paul St. Armad, M.D., an endocrinologist at UCLA, has successfully treated fibromyalgia with uricosuric (gout) drugs, especially guaifenesin, a drug used to liquefy mucus (Yount, J.J. *et al.*, *Women's Health Digest* 3(2) 1997). Dr. Armad has

15 found that such gout drugs provide an effective treatment for fibromyalgia, even though gout and fibromyalgia have no connection. Dr. Armad has found that 24-hour urine samples taken from patients before and after treatment exhibited a significant increase in the excretion of phosphate and a moderate increase of oxalate and calcium after guaifenesin was started. His hypothesis is that an excess of intracellular

20 phosphate, and possibly oxalate, builds up in the cells of fibromyalgia sufferers and depresses formation of energy (ATP) in the mitochondria of the cells. It should be noted that the role of ATP in Dr. Armad's theory is as an energy source and not an agonist of the P2Y₂ receptor.

 Current therapies for increasing vaginal moisture are: lubricating agents

25 such as lubricating creams or jellies, topical estrogen creams, and HRT (hormone replacement therapy). Lubricating jellies provide short-lived and temporary relief, as these are aqueous preparations containing no pharmacologically active agent. Topical estrogen creams, if used on a regular basis, may be absorbed into the systemic circulation. This can cause endometrial stimulation and can lead to endometrial

hyperplasia and carcinoma (Whitehead, M., *et al.*, *N. Eng. J. Med.* 305:1599-1605 (1981)). HRT is effective at relieving symptoms of vaginal atrophy and hence vaginal dryness but has several contraindications and unwanted risks and side effects. A history of gall bladder disease (*N. Eng. J. Med.*, 290:15-19 (1974)) or a personal or
5 family history of reproductive or breast cancer (Harlap, S., *Am. J. Obstet. Gynecol.* 166:1986-1992 (1992)) are contraindications for estrogen therapy. Other contraindications are: history of stroke, cardiovascular disease, deep-vein thrombosis, superficial thrombophlebitis, liver disease, heavy smoking, high blood pressure, diabetes, uterine bleeding or large fibroids, hyperlipidemia, and gross obesity
10 (Lichtman, R., *J. Nurse Midwifery* 36:30-48 (1991)). One major disadvantage of HRT is the resumption of monthly withdrawal bleeds, which many postmenopausal women will not accept. Some women, even while on HRT, still experience a degree of vaginal dryness (Key, E., *Nurs. Stand.* 5:24-27 (1991)).

It has been shown that uridine 5'-triphosphate (UTP) and dinucleotides
15 such as diuridine tetraphosphate are potent agonists of P2Y₂ purinergic receptors found on the surface of human airway epithelium. UTP has been shown to increase both the rate and total amount of mucin secreted by goblet cells *in vitro* (Lethem, M., *et al.*, *Am. J. Respir. Cell Mol. Biol.* 9:315-322 (1993)). UTP has also been shown to increase chloride secretion, and hence, water secretion from airway epithelial cells *in*
20 *vitro* (Mason, S., *et al.*, *Br. J. Pharmacol.* 103:1649-1656 (1991)).

Thus, as a result of the ineffectiveness and risks of current therapies, medical researchers have sought to develop alternatives for the treatment of vaginal dryness. Because of the demonstrated ability of UTP and dinucleotides, such as diuridine tetraphosphate, to increase hydration of airway epithelial secretions and
25 stimulate release of mucins, applicants were motivated to investigate whether UTP and other P2Y₂ and/or P2Y₄ purinergic receptor agonists could stimulate hydration and mucin production in the vaginal and cervical epithelia.

Summary of the Invention

A method of stimulating cervical and vaginal secretions in a subject in need of such treatment is disclosed. The method of the present invention may be used to increase cervical and vaginal secretions for any reason, including, but not limited to, treatment of vaginal dryness and/or treatment of vulvar pain. Vaginal dryness is associated with but not limited to menopause, childbirth, breastfeeding, chemotherapy or radiotherapy, diabetes mellitus, Sjögren's syndrome, Ehlers-Danlos syndrome, systemic sclerosis and other systemic autoimmune diseases, hysterectomy, urogenital surgery, psychosomatic disorders, anxiety, psychosexual problems, and pharmacological drug-related side effects. The method of the present invention comprises administering a P2Y₂ and/or P2Y₄ purinergic receptor agonist: uridine 5'-triphosphate, P¹,P⁴-di(uridine-5')tetraphosphate, cytidine 5'-triphosphate or adenosine 5'-triphosphate or analogs thereof, in an amount effective to stimulate vaginal and cervical secretions.

Another aspect of the present invention is the use of uridine 5'-triphosphate, P¹,P⁴-di(uridine-5')tetraphosphate, cytidine 5'-triphosphate or adenosine 5'-triphosphate or analogs thereof, for the manufacture of a medicament for carrying out a therapeutic method of treatment as given above.

The present invention also discloses pharmaceutical compositions comprising uridine 5'-triphosphate, P¹,P⁴-di(uridine-5')tetraphosphate, cytidine 5'-triphosphate or adenosine 5'-triphosphate or analogs thereof, with a pharmaceutical carrier therefor.

DETAILED DESCRIPTION OF THE INVENTION

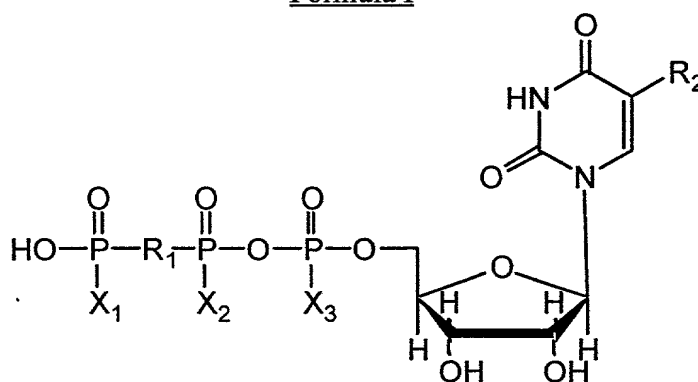
Applicants have discovered that uridine 5'-triphosphate (UTP) and related compounds are potent agonists for purinergic receptors found in cervical and vaginal epithelia preparations. The methods of the present invention are an improvement upon the current most commonly used treatments of vaginal dryness as UTP stimulates a patient's own production and secretion of mucins as well as increasing the levels of mucosal hydration, which serve to maintain the natural protective and

lubricant characteristics of vaginal and cervical mucosa. The methods of the present invention may also be used exclusive of, or as an adjunct to, hormone replacement therapy (HRT) or estrogen replacement therapy (ERT).

The present invention provides a method of stimulating cervical and vaginal secretions in a mammal, including a human, in need thereof by administering an amount of a compound of Formulas I, II, III, or IV or a pharmaceutically acceptable ester or salt thereof effective to increase said secretions.

UTP and its analogs are depicted in general Formula I:

Formula I



10

wherein:

X₁, X₂ and X₃ are each independently either O⁻ or S⁻; preferably, X₂ and X₃ are O⁻;

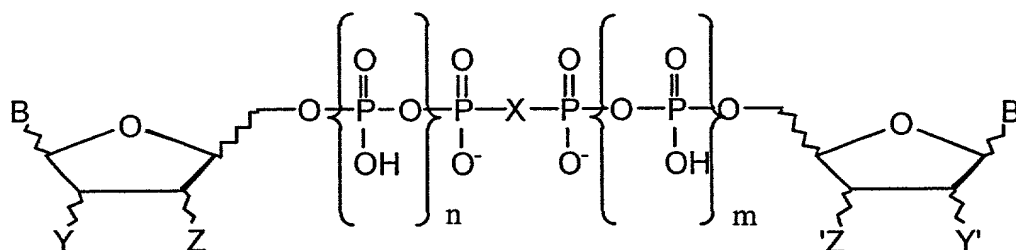
R₁ is O, imido, methylene or dihalomethylene (e.g., dichloromethylene or difluoromethylene); preferably, R₁ is oxygen or difluoromethylene;

R₂ is H or Br; preferably, R₂ is H; particularly preferred compounds of Formula I are uridine 5'-triphosphate (UTP) and uridine 5'-O-(3-thiotriphosphate) (UTP_γS).

A dinucleotide is depicted by the general Formula II:

20

Formula II



wherein:

X is oxygen, methylene, difluoromethylene, imido;

5 $n = 0, 1, \text{ or } 2;$

$m = 0, 1, \text{ or } 2;$

$n + m = 0, 1, 2, 3, \text{ or } 4;$ and

B and B' are each independently a purine residue or a pyrimidine residue
linked through the 9- or 1- position, respectively;

10 $Z = \text{OH or } \text{N}_3;$

$Z' = \text{OH or } \text{N}_3;$

$Y = \text{H or OH};$

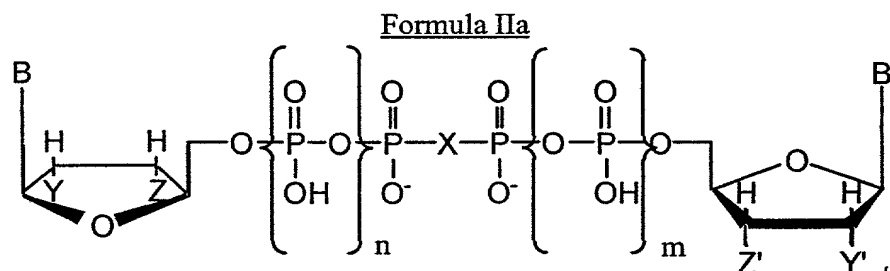
$Y' = \text{H or OH};$

provided that when Z is N_3 , Y is H or when Z' is N_3 , Y' is H.

15 The furanose sugar is preferably in the β -configuration.

The furanose sugar is most preferably in the β -D-configuration.

Preferred compounds of Formula II are the compounds of Formula IIa:



20 wherein:

$X = \text{O};$

$n + m = 1 \text{ or } 2;$

Z, Z', Y, and Y'=OH;

B and B' are defined in Formulas IIc and IId; 6 ✓

5

X=O;

n+m=3 or 4;

Z, Z', Y, and Y'=OH;

B=uracil;

B' is defined in Formulas IIc and IId; or

10

X=O;

n+m=1 or 2;

Z, Y, and ~~Z~~Y'=OH;

~~Y~~ Z'=H;

B=uracil;

15

B' is defined in Formulas IIc and IId; or

X=O;

n+m=0, 1, or 2;

Z and Y=OH;

Z'=N₃;

20

Y'=H;

B=uracil;

B'=thymine; or

X=O;

n+m=0, 1, or 2;

25

Z and Z'=N₃;

Y and Y'=H;

B and B'=thymine; or

X=CH₂, CF₂, or NH;

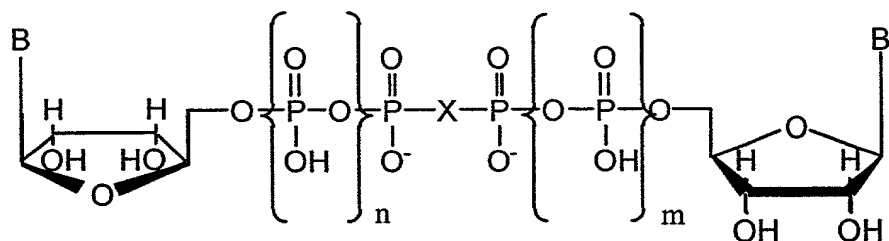
n and m=1;

Z, Z', Y, and Y'=OH;

B and B' are defined in Formulas IIc and IId.

Another preferred group of the compounds of Formula II are the compounds of Formula IIb or the pharmaceutically acceptable salts thereof:

5 Formula IIb



wherein:

10 X is oxygen, methylene, difluoromethylene, or imido;

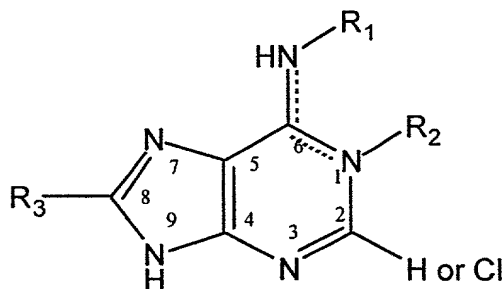
n = 0 or 1;

m = 0 or 1;

n + m = 0, 1, or 2; and

15 B and B' are each independently a purine residue, as in Formula IIc, or a pyrimidine residue, as in Formula IId, linked through the 9- or 1- position, respectively. In the instance where B and B' are uracil, attached at N-1 position to the ribosyl moiety, then the total of m + n may equal 3 or 4 when X is oxygen. The ribosyl moieties are in the D- configuration, as shown, but may be L-, or D- and L-. The D- configuration is preferred.

20 Formula IIc



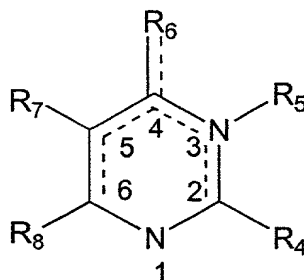
The substituted derivatives of adenine include adenine 1-oxide; 1,N6-(4- or 5-substituted etheno) adenine; 6-substituted adenine; or 8-substituted aminoadenine, where R' of the 6- or 8-HNR' groups are chosen from among:

- 5 arylalkyl (C₁₋₆) groups with the aryl moiety optionally functionalized as described below; alkyl; and alkyl groups with functional groups therein, such as: ([6-aminohexyl]carbamoylmethyl)-, and ω-acylated-amino(hydroxy, thiol and carboxy) derivatives where the acyl group is chosen from among, but not limited to, acetyl, trifluoroacetyl, benzoyl, substituted-benzoyl, etc., or the carboxylic moiety is
10 present as its ester or amide derivative, for example, the ethyl or methyl ester or its methyl, ethyl or benzamido derivative. The ω-amino(hydroxy, thiol) moiety may be alkylated with a C₁₋₄ alkyl group.

Likewise, B or B' or both in Formula IIb may be a pyrimidine with the general formula of Formula IIc, linked through the 1-position:

15

Formula IIc



wherein:

- R₄ is hydroxy, mercapto, amino, cyano, aralkoxy, C₁₋₆ alkoxy, C₁₋₆ alkylamino, and dialkylamino, the alkyl groups optionally linked to form a
20 heterocycle;

R₅ is hydrogen, acyl, C₁₋₆ alkyl, aroyl, C₁₋₅ alkanoyl, benzoyl, or sulphonate;

R₆ is hydroxy, mercapto, alkoxy, aralkoxy, C₁₋₆-alkylthio, C₁₋₅ disubstituted amino, triazolyl, alkylamino, or dialkylamino, where the alkyl groups are optionally linked to form a heterocycle or linked to N-3 to form an optionally substituted ring;

5 R₇ is hydrogen, hydroxy, cyano, nitro, alkenyl, with the alkenyl moiety optionally linked through oxygen to form a ring optionally substituted on the carbon adjacent to the oxygen with alkyl or aryl groups, substituted alkynyl or hydrogen where R₈ is amino or substituted amino and halogen, alkyl, substituted alkyl, perhalomethyl (e.g., CF₃), C₂₋₆ alkyl, C₂₋₃ alkenyl, or substituted ethenyl (e.g., allylamino, bromvinyl and ethyl propenoate, or propenoic acid), C₂₋₃ alkynyl or
10 substituted alkynyl when R₆ is other than amino or substituted amino and together R₅ - R₆ may form a 5- or 6-membered saturated or unsaturated ring bonded through N or O at R₆, such a ring may contain substituents that themselves contain functionalities;

 R₈ is hydrogen, alkoxy, arylalkoxy, alkylthio, arylalkylthio,
15 carboxamidomethyl, carboxymethyl, methoxy, methylthio, phenoxy, or phenylthio.

 In the general structure of Formula IIc above, the dotted lines in the 2- to 6-positions are intended to indicate the presence of single or double bonds in these positions; the relative positions of the double or single bonds being determined by whether the R₄, R₆, and R₇ substituents are capable of keto-enol tautomerism.

20 In the general structures of Formula IIc and IId above, the acyl groups advantageously comprise alkanoyl or aroyl groups. The alkyl groups advantageously contain 1 to 8 carbon atoms, particularly 1 to 4 carbon atoms optionally substituted by one or more appropriate substituents, as described below. The aryl groups including the aryl moieties of such groups as aryloxy are preferably phenyl groups optionally
25 substituted by one or more appropriate substituents, as described below. The above mentioned alkenyl and alkynyl groups advantageously contain 2 to 8 carbon atoms, particularly 2 to 6 carbon atoms, e.g., ethenyl or ethynyl, optionally substituted by one or more appropriate substituents as described below. Appropriate substituents on the above-mentioned alkyl, alkenyl, alkynyl, and aryl groups are advantageously selected

from halogen, hydroxy, C₁₋₄ alkoxy, C₁₋₄ alkyl, C₆₋₁₂ arylalkoxy, carboxy, cyano, nitro, sulfonamido, sulfonate, phosphate, sulfonic, amino, and substituted amino wherein the amino is singly or doubly substituted by a C₁₋₄ alkyl, and when doubly substituted, the alkyl groups optionally being linked to form a heterocycle.

5 For purposes of further clarifying the foregoing descriptions of Formulae IIc and IId, the descriptions can be simplified to the following:

R₂ is O or is absent; or

R₁ and R₂ taken together may form optionally substituted 5-membered fused imidazole ring; or

10 R₁ of the 6-HNR₁ group or R₃ of the 8-HNR₃ group is chosen from the group consisting of:

(a) arylalkyl (C₁₋₆) groups with the aryl moiety optionally substituted,

(b) alkyl,

15 (c) ([6-aminohexyl]carbamoylethyl),

(d) ω-amino alkyl (C₂₋₁₀),

(e) ω-hydroxy alkyl (C₂₋₁₀),

(f) ω-thiol alkyl (C₂₋₁₀),

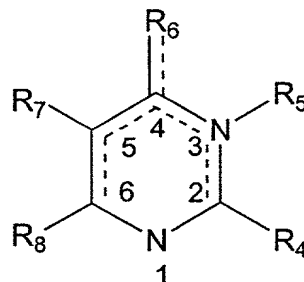
(g) ω-carboxy alkyl (C₂₋₁₀),

20 (h) the ω-acylated derivatives of (b), (c) or (d) wherein the acyl group is either acetyl, trifluoroacetyl, benzoyl, or substituted-benzoyl alkyl(C₂₋₁₀), and

(i) ω-carboxy alkyl (C₂₋₁₀) as in (e) above wherein the carboxylic moiety is an ester or an amide;

25

Formula IId



wherein:

R₄ is hydroxy, mercapto, amino, cyano, aralkoxy, C₁₋₆ alkylthio, C₁₋₆ alkoxy, C₁₋₆ alkylamino or dialkylamino, wherein the alkyl groups of said dialkylamino are optionally linked to form a heterocycle;

R₅ is hydrogen, acyl, C₁₋₆ alkyl, aroyl, C₁₋₅ alkanoyl, benzoyl, or sulphonate;

R₆ is hydroxy, mercapto, alkoxy, aralkoxy, C₁₋₆-alkylthio, C₁₋₅ disubstituted amino, triazolyl, alkylamino or dialkylamino, wherein the alkyl groups of said dialkylamino are optionally linked to form a heterocycle or linked to N³ to form an optionally substituted ring;

R₅ - R₆ together forms a 5 or 6-membered saturated or unsaturated ring bonded through N or O at R₆, wherein said ring is optionally substituted;

R₇ is selected from the group consisting of:

- (a) hydrogen,
- (b) hydroxy,
- (c) cyano,
- (d) nitro,
- (e) alkenyl, wherein the alkenyl moiety is optionally linked through oxygen to form a ring optionally substituted with alkyl or aryl groups on the carbon adjacent to the oxygen,
- (f) substituted alkynyl
- (g) halogen,

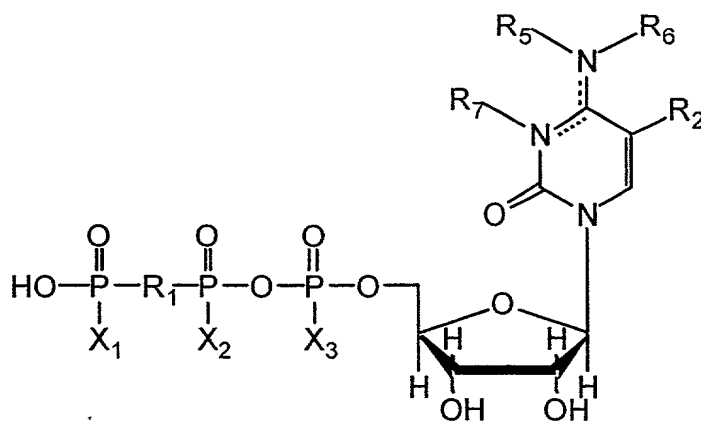
- (h) alkyl,
- (i) substituted alkyl,
- (j) perhalomethyl,
- (k) C₂₋₆ alkyl,
- (l) C₂₋₃ alkenyl,
- (m) substituted ethenyl,
- (n) C₂₋₃ alkynyl and
- (o) substituted alkynyl when R₆ is other than amino or substituted amino;

R₈ is selected from the group consisting of:

- (a) hydrogen,
- (b) alkoxy,
- (c) arylalkoxy,
- (d) alkylthio,
- (e) arylalkylthio,
- (f) carboxamidomethyl,
- (g) carboxymethyl,
- (h) methoxy,
- (i) methylthio,
- (j) phenoxy and
- (k) phenylthio.

CTP and its analogs are depicted by general Formula III:

Formula III



wherein:

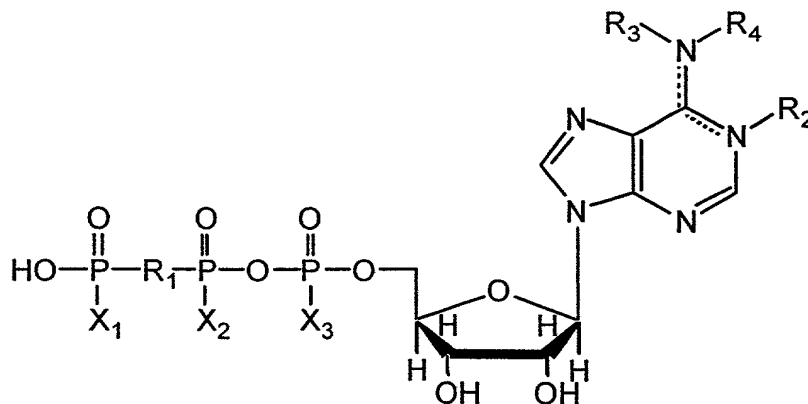
R_1 , X_1 , X_2 and X_3 are defined as in Formula I;

- 5 R_5 and R_6 are H while R_7 is nothing and there is a double bond between N-3 and C-4 (cytosine), or

R_5 , R_6 and R_7 taken together are $-CH=CH-$, forming a ring from N-3 to N-4 with a double bond between N-4 and C-4 (3, N^4 -ethenocytosine) optionally substituted at the 4- or 5-position of the etheno ring.

- 10 ATP and its analogs are depicted by general Formula IV:

Formula IV



- 15 wherein:

R_1 , X_1 , X_2 , and X_3 are defined as in Formula I;

R₃ and R₄ are H while R₂ is nothing and there is a double bond between N-1 and C-6 (adenine), or

R₃ and R₄ are H while R₂ is O and there is a double bond between N-1 and C-6 (adenine 1-oxide), or

5 R₃, R₄, and R₂ taken together are -CH=CH-, forming a ring from N-6 to N-1 with a double bond between N-6 and C-6 (1,N6-ethenoadenine).

For simplicity, Formulas I, II, III, and IV herein illustrate the active compounds in the naturally occurring D-configuration, but the present invention also encompasses compounds in the L-configuration, and mixtures of compounds in the D- and L-configurations, unless otherwise specified. The naturally occurring
10 D-configuration is preferred.

The compounds of the invention may be present in the form of their pharmaceutically acceptable salts, such as, but not limited to, an alkali metal salt such as sodium or potassium; an alkaline earth metal salt such as manganese, magnesium,
15 or calcium; or an ammonium or tetraalkyl ammonium salt, i.e., NX₄⁺ (wherein X is C₁₋₄). Pharmaceutically acceptable salts are salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects. The compounds of the invention may also be present in the form of prodrugs, typically comprising esters or amide moieties on the heterocyclic and furanosyl
20 hydroxyls of the compound.

Another aspect of the present invention is a method of treating a mammal with vaginal dryness arising from, but not limited to, menopause, childbirth, breastfeeding, chemotherapy or radiotherapy, diabetes mellitus, Sjögren's syndrome, Ehlers-Danlos syndrome, systemic sclerosis and other systemic autoimmune diseases,
25 hysterectomy, urogenital surgery, psychosomatic disorders, anxiety, psychosexual problems, and pharmacological drug-related side effects.

It is also contemplated that the method of the present invention can be used to increase vaginal moisture and lubrication in healthy women for the purpose of facilitating sexual intercourse. It is further contemplated that the method of the

present invention would be particularly useful for a woman who wished to accommodate a sexual partner who is undergoing treatment with Viagra® or other such drugs used for the treatment of erectile dysfunction.

The present invention further provides pharmaceutical compositions comprising a dosage form containing either P2Y₂ and/or P2Y₄ purinergic receptor agonists selected from the group consisting of general Formula I, i.e., uridine 5'-triphosphate [UTP] and its analogs, general Formula II, i.e., P¹,P⁴-di(uridine-5') tetraphosphate [U₂P₄] and its analogs, general Formula III, i.e., cytidine 5'-triphosphate [CTP] and its analogs, and general Formula IV, i.e., adenosine 5'-triphosphate [ATP] and its analogs.

The compounds disclosed herein may be administered to the cervical and/or vaginal mucosa of a patient by any suitable means, but are preferably administered by a solution, gel, suspension, cream, foam, pessary, or tablet containing the active compound. Alternatively, the active compounds may be administered by continuous release from a vaginal ring (Stumpf, P., *Obstet. Gynecol.* 75:9S (1990)) or an intrauterine device (Andersson, K., *et al.*, *Obstet. Gynecol.* 79:963 (1992)).

The topical solution, gel, jelly, ointment, cream, foam, pessary, or tablet contain the active compound in a physiologically compatible vehicle, as those skilled in the art of gynecological topical delivery system development can select using conventional criteria.

Solutions formulated for administration to the vagina are usually referred to as irrigations. These are sterile solutions, prepared in a manner typical of sterile injections that are intended for prepared as a single use sterile solution.

Gels or jellies may be produced using a suitable gelling agent including, but not limited to, gelatin, tragacanth, or a cellulose derivative and may include glycerol as a humectant, emollient, and preservative.

Ointments are semi-solid preparations that consist of the active ingredient incorporated into a fatty, waxy, or synthetic base.

Examples of suitable creams include, but are not limited to, water-in-oil and oil-in-water emulsions. Water-in-oil creams may be formulated by using a suitable emulsifying agent with properties similar, but not limited, to those of the fatty alcohols such as cetyl alcohol or cetostearyl alcohol and to emulsifying wax. Oil-in-
5 water creams may be formulated using an emulsifying agent such as cetomacrogol emulsifying wax. Suitable properties include the ability to modify the viscosity of the emulsion and both physical and chemical stability over a wide range of pH. The water soluble or miscible cream base may contain a preservative system and may also be buffered to maintain an acceptable physiological pH.

10 Foam preparations may be formulated to be delivered from a pressurized aerosol canister, via a suitable applicator, using inert propellants. Suitable excipients for the formulation of the foam base include, but are not limited to, propylene glycol, emulsifying wax, cetyl alcohol, and glyceryl stearate. Potential preservatives include methylparaben and propylparaben.

15 Pessaries are solid unit-dose forms suitably shaped for insertion into the vagina and may either be composed of a base that melts at body temperature or which dissolves when in contact with mucous secretions. Examples of suitable bases include, but are not limited to, theobroma oil, synthetic fat bases (e.g. Witepsol), polyethylene glycols (macrogols), and glycerol suppository basis.

20 Vaginal tablets are composed of the active ingredient contained within a solid dosage form base which may include, but not be limited to, excipients such as lactose, microcrystalline cellulose, corn starch, magnesium stearate, silicon dioxide, and hydroxypropyl methylcellulose.

In addition to the topical method of administration described above, there
25 are various methods of administering the compounds of the present invention systemically. One such means would involve an aerosol suspension of respirable particles comprised of the active compound, which the subject inhales. The active compound would be absorbed into the bloodstream via the lungs and contact the cervical and/or vaginal tissues in a pharmaceutically effective amount. The respirable

particles may be liquid or solid, with a particle size sufficiently small to pass through the mouth and larynx upon inhalation; in general, particles ranging from about 1 to 10 microns, but more preferably 1-5 microns, in size are considered respirable.

Another means of systemically administering the active compounds to the cervical and vaginal tissues of the subject would involve administering a liquid/liquid suspension in the form of nasal drops of a liquid formulation, or a nasal spray of respirable particles which the subject inhales. Liquid pharmaceutical compositions of the active compound for producing a nasal spray or nasal drops may be prepared by combining the active compound with a suitable vehicle, such as sterile pyrogen free water or sterile saline by techniques known to those skilled in the art.

Other means of systemic administration of the active compound would involve oral administration, in which pharmaceutical compositions containing compounds of Formulas I, II, III, or IV are in the form of tablets, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents, and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with nontoxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate, or sodium phosphate; granulating and disintegrating agents, for example, corn starch or alginic acid; binding agents, for example, starch, gelatin, or acacia; and lubricating agents, for example magnesium stearate, stearic acid, or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. Formulations for oral

use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate, or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.

5 Additional means of systemic administration of the active compound to the cervical and vaginal tissues of the subject would involve a suppository form of the active compound, such that a therapeutically effective amount of the compound reaches the cervical and vaginal tissues via systemic absorption and circulation.

The quantity of the active compound included in the pharmaceutical
10 composition is an amount sufficient to achieve concentrations of the active compound on the cervical and/or vaginal mucosa of the subject of from about 10^{-7} to about 10^{-1} Moles/liter, and more preferably from about 10^{-6} to about 10^{-1} Moles/liter.

Depending on the solubility of the particular formulation of active
compound administered, the daily dose to promote cervical and/or vaginal mucin
15 production and/or hydration may be divided among one or several unit dose administrations. The total daily dose for UTP (for example) may range from 1 to 1000 milligrams, depending upon the age and state of the subject, given at a regimen of up to four times per day or on an as needed basis to address acute exacerbations.

Some compounds of Formulas I, II, III, and IV can be made by methods
20 which are well known to those skilled in the art and in accordance with known procedures (Zamecnik, P., *et al.*, *Proc. Natl Acad. Sci. USA* 89:2370-2373 (1992); Ng, K., *et al.*, *Nucleic Acids Res.* 15:3572-3580 (1977); Jacobus, K.M., *et al.*, U.S. Patent No. 5,789,391 and Pendergast, W., *et al.*, International Patent Application WO98/34942)); some are commercially available, for example, from Sigma Chemical
25 Company, PO Box 14508, St. Louis, MO 63178. The synthetic methods of U.S. Patent 5,789,391 and International Patent Application WO98/34942 are incorporated herein by reference.

Examples

Example 1: In Vitro short circuit (I_{sc}) measurements

The compound UTP is a potent agonist of P2Y₂ and/or P2Y₄ purinergic receptors in cervical and vaginal tissue preparations by evaluation *in vitro* by administering UTP to the tissue culture sufficient to achieve concentrations of UTP on the mucosa of from about 10^{-7} to about 10^{-1} moles/liter. (Rojanasakul, Y., *et al.*, *Pharm. Res.* 9:1029-34 (1992); Bechgaard, E., *et al.*, *Int. J. Pharm.* 106:237-242 (1994); Gipson, I., *et al.*, *Biol. Reprod.* 56:999-1011, (1997)). Specifically, ovariectomized female white albino New Zealand rabbits are sacrificed and vaginal tissue is removed. The tissue is mounted on a supporting ring and clamped in an Ussing chamber. I_{sc} is measured as flowing from the epithelial side to the serosal side of the tissue. Approximately half of this current corresponds to chloride movement through the membrane and hence, this is an accurate measure of the corresponding fluid movement.

Example 2. In vivo study in rabbits

The compounds of the invention are evaluated *in vivo* by administering UTP, or any of the other P2Y₂ and/or P2Y₄ agonists of the present invention to an animal in an amount sufficient to achieve concentrations of P2Y₂ and/or P2Y₄ agonist on the cervical and/or vaginal mucosa of the animal of from about 10^{-7} to about 10^{-1} moles/liter (Richardson, J., *et al.*, *Int. J. Pharm.* 56:29-35 (1989)). Specifically, ovariectomized female white albino New Zealand rabbits are dosed with a P2Y₂ and/or P2Y₄ agonist such as any of the compounds of the present invention. A vaginal smear is then obtained with a cotton swab. The sample is appropriately prepared, an ELISA or a colorimetric dot blot method is run on the sample, and the relative amounts of representative cervical mucins are determined as compared to non-ovariectomized controls. (Gipson, I. *et al.*, *Biol. Reprod.* 56:999-1011 (1997)).

Example 3. In vivo study using ovariectomized cynologous monkeys

The compounds of the present invention are evaluated *in vivo* with an animal model of vaginal dryness as follows. Ovariectomized cynomolgus monkeys are

examined before treatment and graded subjectively using a fabinal atrophy index.

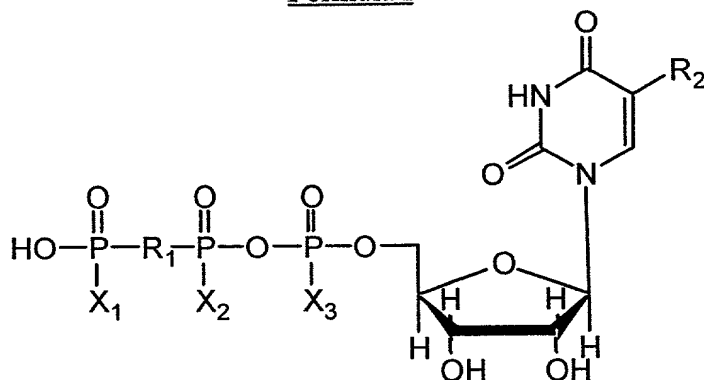
The animals were then dosed intravaginally with 100 to 300 μ l mist containing 10^{-2} to 1 moles/liter P2Y₂ and/or P2Y₄ agonist, such as any of the compounds of the present invention. After 10, 20, 30, 60 and 90 minutes the animals are subjected to a

- 5 gynecological exam and graded by qualified medical professions with the vaginal atrophy index on a scale of 1 to 5, including a measurement of fluid pH. (Hubbard, G. *et al.*, *Lab Animal Sci.* 47, 36-39, (1997)).

WHAT IS CLAIMED IS:

1. A method of stimulating cervical and vaginal secretions in a mammal in need thereof by administering an effective secretion stimulating amount of a
5 compound of Formulas I, II, III, or IV:

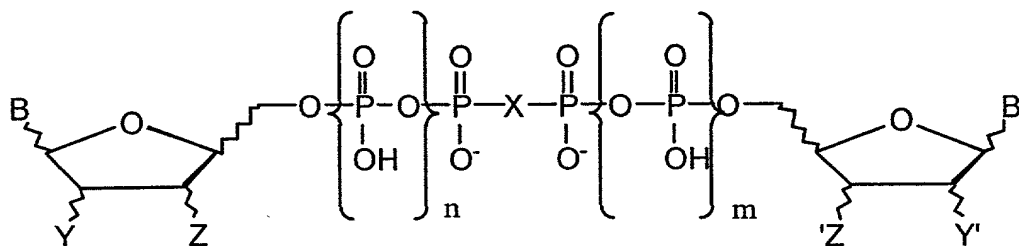
Formula I



wherein:

- 10 X_1 , X_2 and X_3 are each independently either O^- or S^- ;
- R_1 is O, imido, methylene or dihalomethylene;
- R_2 is H or Br; preferably, R_2 is H; or

Formula II



wherein:

- 15 X is oxygen, methylene, difluoromethylene, imido;
- $n = 0, 1, \text{ or } 2$;
- 20 $m = 0, 1, \text{ or } 2$;

$n + m = 0, 1, 2, 3, \text{ or } 4$; and

B and B' are each independently a purine residue or a pyrimidine residue
linked through the 9- or 1- position, respectively;

Z = OH or N₃;

5 Z' = OH or N₃;

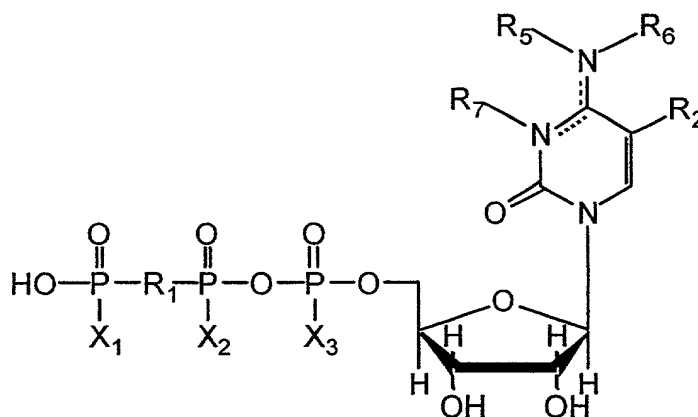
Y = H or OH;

Y' = H or OH;

provided that when Z is N₃, Y is H or when Z' is N₃, Y' is H; or

Formula III

10



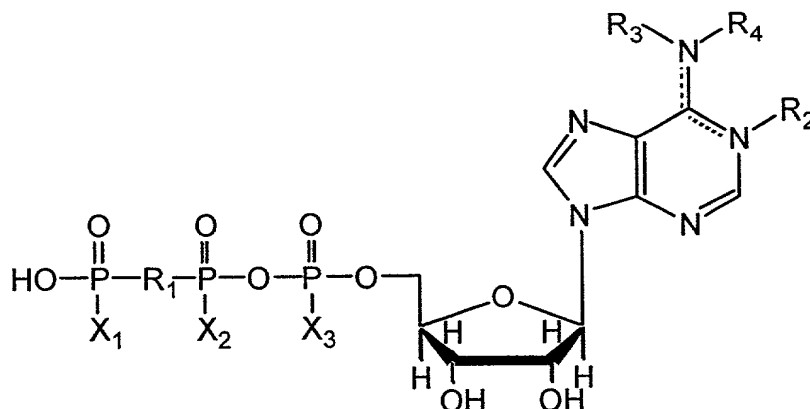
wherein:

R₁, X₁, X₂ and X₃ are defined as in Formula I;

15 R₅ and R₆ are H while R₇ is nothing and there is a double bond between
N-3 and C-4 (cytosine), or

R₅, R₆ and R₇ taken together are -CH=CH-, forming a ring from N-3 to
N-4 with a double bond between N-4 and C-4 (3,N⁴-ethenocytosine) optionally
substituted at the 4- or 5-position of the etheno ring; or

Formula IV

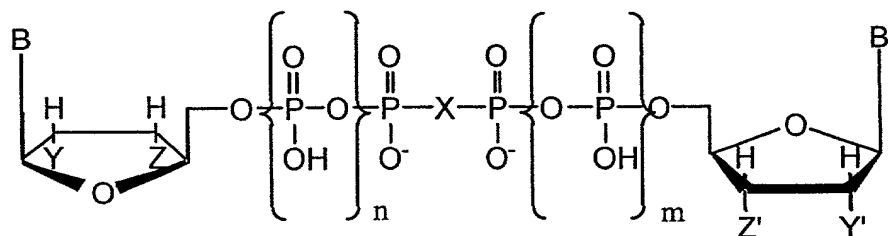


wherein:

- 5 R_1 , X_1 , X_2 , and X_3 are defined as in Formula I;
 R_3 and R_4 are H while R_2 is nothing and there is a double bond between N-1 and C-6 (adenine), or
 R_3 and R_4 are H while R_2 is O and there is a double bond between N-1 and C-6 (adenine 1-oxide), or
 R_3 , R_4 , and R_2 taken together are $-\text{CH}=\text{CH}-$, forming a ring from N-6 to N-1 with a double bond between N-6 and C-6 (1,N6-ethenoadenine);
 or pharmaceutically acceptable esters or salts thereof.

2. The method of claim 1 wherein the compounds of Formula II are those of Formula IIa:

Formula IIa



wherein:

- 20 $X=\text{O}$;

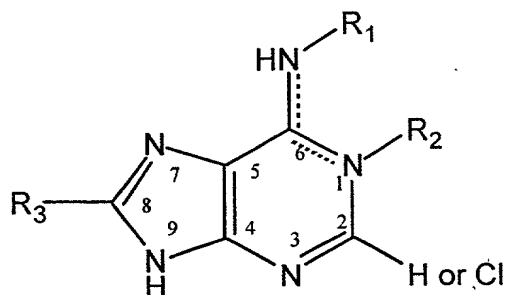
$n+m=1$ or 2 ;

$Z, Z', Y,$ and $Y'=OH$;

B and B' are defined in Formulas IIc and IId:

5

Formula IIc



R_2 is O or is absent; or

10

R_1 and R_2 taken together may form optionally substituted 5-membered fused imidazole ring; or

R_1 of the $6-HNR_1$ group or R_3 of the $8-HNR_3$ group is chosen from the group consisting of:

15

(a) arylalkyl (C_{1-6}) groups with the aryl moiety optionally substituted,

(b) alkyl,

(c) ([6-aminoethyl]carbamoylethyl),

(d) ω -amino alkyl (C_{2-10}),

(e) ω -hydroxy alkyl (C_{2-10}),

20

(f) ω -thiol alkyl (C_{2-10}),

(g) ω -carboxy alkyl (C_{2-10}),

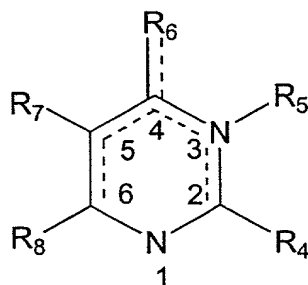
(h) the ω -acylated derivatives of (b), (c) or (d) wherein the acyl group is either acetyl, trifluoroacetyl, benzoyl, or substituted-benzoyl alkyl(C_{2-10}), and

25

(i) ω -carboxy alkyl (C_{2-10}) as in (e) above wherein the

carboxylic moiety is an ester or an amide;

Formula II



5 wherein:

 R₄ is hydroxy, mercapto, amino, cyano, aralkoxy, C₁₋₆ alkylthio, C₁₋₆ alkoxy, C₁₋₆ alkylamino or dialkylamino, wherein the alkyl groups of said dialkylamino are optionally linked to form a heterocycle;

 R₅ is hydrogen, acyl, C₁₋₆ alkyl, aroyl, C₁₋₅ alkanoyl, benzoyl, or
10 sulphonate;

 R₆ is hydroxy, mercapto, alkoxy, aralkoxy, C₁₋₆-alkylthio, C₁₋₅ disubstituted amino, triazolyl, alkylamino or dialkylamino, wherein the alkyl groups of said dialkylamino are optionally linked to form a heterocycle or linked to N³ to form an optionally substituted ring;

15 R₅ - R₆ together forms a 5 or 6-membered saturated or unsaturated ring bonded through N or O at R₆, wherein said ring is optionally substituted;

 R₇ is selected from the group consisting of:

- (a) hydrogen,
- (b) hydroxy,
- 20 (c) cyano,
- (d) nitro,
- (e) alkenyl, wherein the alkenyl moiety is optionally linked through oxygen to form a ring optionally substituted with alkyl or aryl groups on the carbon adjacent to the oxygen,

(f) substituted alkynyl

(g) halogen,

(h) alkyl,

(i) substituted alkyl,

5 (j) perhalomethyl,

(k) C₂₋₆ alkyl,

(l) C₂₋₃ alkenyl,

(m) substituted ethenyl,

(n) C₂₋₃ alkynyl and

10 (o) substituted alkynyl when R₆ is other than amino or substituted amino;

R₈ is selected from the group consisting of:

(a) hydrogen,

(b) alkoxy,

15 (c) arylalkoxy,

(d) alkylthio,

(e) arylalkylthio,

(f) carboxamidomethyl,

(g) carboxymethyl,

20 (h) methoxy,

(i) methylthio,

(j) phenoxy and

(k) phenylthio.

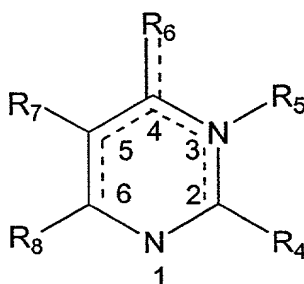
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wherein the substituted derivatives of adenine are adenine 1-oxide; 1,N6-(4- or 5-substituted etheno) adenine; 6-substituted adenine; or 8-substituted aminoadenine, where R' of the 6- or 8-HNR' groups are chosen from among: arylalkyl (C₁₋₆) groups with the aryl moiety optionally functionalized; alkyl; and alkyl

groups with functional groups therein, selected from the group consisting of ([6-aminohexyl]carbamoylmethyl)-, and ω -acylated-amino(hydroxy, thiol and carboxy) derivatives where the acyl group is acetyl, trifluoroacetyl, benzoyl or substituted-benzoyl and the carboxylic moiety is present as the ethyl or methyl ester derivative or the methyl, ethyl or benzamido derivative;

B or B' or both in Formula IIb may be a pyrimidine with the general formula of Formula IId, linked through the 1-position:

Formula IId



wherein:

10 R_4 is hydroxy, mercapto, amino, cyano, aralkoxy, C_{1-6} alkoxy, C_{1-6} alkylamino, and dialkylamino, the alkyl groups optionally linked to form a heterocycle;

R_5 is hydrogen, acyl, C_{1-6} alkyl, aroyl, C_{1-5} alkanoyl, benzoyl, or sulphonate;

15 R_6 is hydroxy, mercapto, alkoxy, aralkoxy, C_{1-6} -alkylthio, C_{1-5} disubstituted amino, triazolyl, alkylamino, or dialkylamino, where the alkyl groups are optionally linked to form a heterocycle or linked to N-3 to form an optionally substituted ring;

20 R_7 is hydrogen, hydroxy, cyano, nitro, alkenyl, with the alkenyl moiety optionally linked through oxygen to form a ring optionally substituted on the carbon adjacent to the oxygen with alkyl or aryl groups, substituted alkynyl or hydrogen where R_8 is amino or substituted amino and halogen, alkyl, substituted alkyl, perhalomethyl, C_{2-6} alkyl, C_{2-3} alkenyl, or ethenyl (optionally substituted by

allylamino, bromvinyl and ethyl propenoate, or propenoic acid), C₂₋₃ alkynyl or substituted alkynyl when R₆ is other than amino or substituted amino and together R₅ - R₆ may form a 5- or 6-membered saturated or unsaturated ring bonded through N or O at R₆, such a ring may contain substituents that themselves contain functionalities;

5 R₈ is hydrogen, alkoxy, arylalkoxy, alkylthio, arylalkylthio, carboxamidomethyl, carboxymethyl, methoxy, methylthio, phenoxy, or phenylthio; or

X=O;

n+m=3 or 4;

10 Z, Z', Y, and Y'=OH;

B=uracil;

B' is defined in Formulas IIc and IId; or

X=O;

15 n+m=1 or 2;

Z, Y, and Y'=OH;

Z'=H;

B=uracil;

B' is defined in Formulas IIc and IId; or

20

X=O;

n+m=0, 1, or 2;

Z and Y=OH;

Z'=N₃;

25 Y'=H;

B=uracil;

B'=thymine; or

X=O;

$n+m=0, 1, \text{ or } 2;$
 $Z \text{ and } Z'=N_3;$
 $Y \text{ and } Y'=H;$
 $B \text{ and } B'=\text{thymine}; \text{ or}$

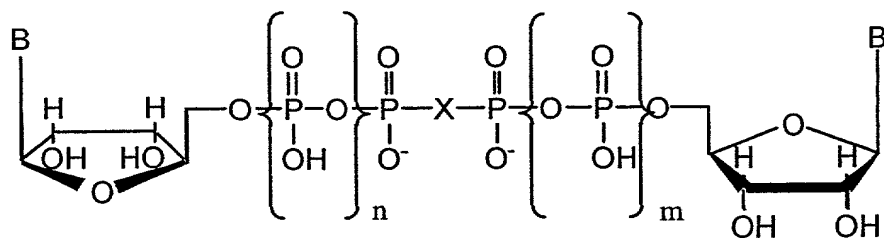
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$X=CH_2, CF_2, \text{ or } NH;$
 $n \text{ and } m=1;$
 $Z, Z', Y, \text{ and } Y'=OH;$
 $B \text{ and } B' \text{ are defined in Formulas IIc and IId.}$

10

3. The method of claim 1 wherein the compounds of Formula II are those of Formula IIb:

Formula IIb



15

wherein:

X is oxygen, methylene, difluoromethylene, or imido;

$n = 0 \text{ or } 1;$

20

$m = 0 \text{ or } 1;$

$n + m = 0, 1, \text{ or } 2; \text{ and}$

25

B and B' are each independently a purine residue, as in Formula IIc as described in claim 2, or a pyrimidine residue, as in Formula IId as described in claim 2, linked through the 9- or 1- position, respectively; provided that when B and B' are uracil, attached at N-1 position to the ribosyl moiety, then the total of $m + n$ equals 3 or 4 when X is oxygen.

4. The method of claim 1 wherein R₂ of Formula I is H.

5. The method of claim 1 wherein the furanose sugar of Formula II is in
5 the β-D-configuration.

6. A method of treating a mammal with vaginal dryness by administering
an effective vaginal dryness treatment amount of a compound of Formulas I, II, III, or
IV as described in claims 1-5.

10

7. A pharmaceutical composition comprising a compound of Formulas I,
II, III, or IV as described in claims 1-5 together with a pharmaceutically acceptable
carrier therefor in the form of a liquid or gel suspension.

15

8. The method of claim 6 wherein the amount of compound of Formulas
I, II, III or IV administered to the mammal is sufficient to achieve a concentration on
the cervical and/or vaginal mucosa of from about 10⁻⁷ moles/liter to about 10⁻¹
moles/liter.

20

9. The method of claim 6 wherein the amount of compound of Formulas
I, II, III, or IV administered to the mammal is sufficient to achieve a daily dose of
between 1 to 1000 milligrams.

10. A method of treating a mammal with vulvar pain by administering an
25 effective vulvar pain treatment amount of a compound of Formulas I, II, III, or IV as
described in claims 1-5.

ABSTRACT

5

COPY

Combined Declaration and Power of Attorney for Patent Application

Docket Number: 3678 0028 US02
USPTO: use "US04"
as new
Docket #

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am an original, first and joint inventor (if plural names are listed below) of the subject matter that is claimed and for which a patent is sought on the invention entitled **METHOD OF PROMOTING CERVICAL AND VAGINAL SECRETIONS**, the specification of which is attached hereto unless the following box is checked:

☒ was filed on November 25, 1998;
as United States Application Number or PCT International Application Number 09/199,912; and
was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information that is material to patentability as defined in 37 C.F.R. § 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT international application, which designated at least one country other than the United States listed below, and have also identified below any foreign application for patent or inventor's certificate, or PCT international application having a filing date before that of the application on which priority is claimed.

PRIOR FOREIGN APPLICATION(S)

Application No.	Country	(Day/Month/Year/Filed)	Priority Claimed
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below.

Application No.	Filing Date
60/054,147	July 25, 1997

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or under § 365(c) of any PCT international application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information that is material to patentability as defined in 37 C.F.R. § 1.56 that became available between the filing date of the prior application and the national or PCT international filing date of this application.

Application No.	Filing Date	(Status – patented, pending, abandoned)
09/122,516	July 24, 1998	Pending

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

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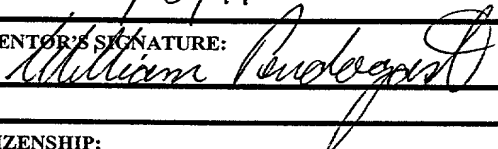
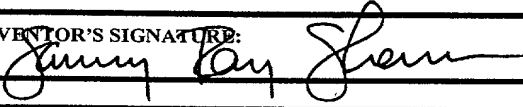
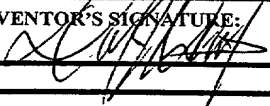

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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(Supply similar information and signature for subsequent joint inventors, if any)